

### **REMARKS**

Applicants have received and reviewed an Office Action dated January 8, 2007. By way of response, Applicants have added new claims 10-14. Claim 10 is supported in the specification at least at page 11, lines 16-17. Claim 11 is supported in the specification at least at page 11, lines 30-31. Claim 12 is supported in the specification at least at page 12, line 22. Claim 13 is supported in the specification at least at page 13, line 13. Claim 14 is supported in the specification at least at page 13, line 27. No new matter is presented. Claims 1-14 are pending. Applicants submit that the pending claims are supported by the specification.

For the reasons given below, Applicants submit that the original and newly presented claims are in condition for allowance and notification to that effect is earnestly solicited.

#### **Rejections under 35 U.S.C. § 103(a)**

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Gall et al., U.S. Patent No. 4,942,157 ("Gall"), Blum et al., U.S. Patent No. 4,407,761 ("Blum"), and Jary et al., U.S. Patent No. 4,304,734 in view of Bosies et al., U.S. Patent No. 5,002,937. Applicants respectfully traverse the rejection.

Sulfolane, or tetrahydrothiophene 1,1-dioxide, has not previously been used as a solvent for the reaction of a carboxylic acid with phosphorous trichloride ( $\text{PCl}_3$ ), phosphorous oxychloride ( $\text{POCl}_3$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ). While Applicants describe other solvents that can be used, "sulfolane was observed to provide superior yields" (page 3, lines 25-26).

Applicants have unexpectedly discovered that using sulfolane as the solvent results in significantly higher yield of a range of pure diphosphonic acid products. Applicants have evidenced their discovery by disclosing a range of products, all of which are obtained at high yield compared to the reaction yields of the art. Example 1 describes synthesis of alendronic acid at 68.5% of theoretical yield of >99.0% pure product (page 11, lines 16-17); Example 2 describes synthesis of pamidronic acid at 62.7% of theoretical yield of >99.0% pure product (page 11, lines 30-31); Example 3 describes synthesis of pamidronic acid at 76.4% of theoretical yield of >99.0% pure product (page 12, lines 7-8); Example 4 describes the synthesis of risedronic acid at 70.47% theoretical yield of >99.0% pure product (page 12, line 22); Example 5

describes the synthesis of risedronic acid at 76.4% of theoretical yield of >99% pure product (page 12, lines 30-31); Example 6 describes the synthesis of zoledronic acid at 70.7% theoretical yield (page 13, line 13) and Example 7 describes the synthesis of zoledronic acid at >99.5% purity (page 13, line 27).

The art teaches that in general, yields of 27% to 56% of theory are obtained for the reaction of a carboxylic acid with phosphorous trichloride ( $\text{PCl}_3$ ), phosphorous oxychloride ( $\text{POCl}_3$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ). Applicants have unexpectedly found that a consistently, repeatably higher yield of product - 62.7% to 76.4% of theory - is obtained when employing sulfolane as the solvent. The discovery of a new use for a known structure based on unknown properties of the structure can be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). In order to be patentable, the properties must be unexpected. MPEP § 2112.02.

The use of sulfolane in Applicants' reaction scheme has provided such an unexpected result. There could be no reasonable expectation, prior to Applicants' discovery, of success in using a particular solvent to realize significantly improved yields over a wide range of reagent species.

Gall states at column 2 line 67 to column 3, line 2 that the reaction of a carboxylic acid to form a diphosphonic acid can be "carried out in the presence of diluents, for example halogenated hydrocarbons, especially chlorobenzene or tetrachloroethane, or also dioxan." Only chlorobenzene is exemplified, in Example 1, col. 4, lines 40-60, wherein only 27% of theoretical yield is obtained (line 58). No solvent is used in Example 2 (column 5, lines 1-14) wherein 35% of theoretical yield is obtained (line 13). No solvent is used in Example 3 (column 5, lines 16-28) wherein 54% of theoretical yield is obtained (line 26). Thus, the use of chlorobenzene actually results in a lower yield than is realized without solvent.

Blum similarly employs only chlorobenzene as the solvent and realizes yields of 56.0% of theoretical yield (column 4, line 1), 45.1% of theoretical yield (column 4, line 24), 97.4% of theoretical yield (column 4, line 40) and 49.8% of theoretical yield (column 4, line 58). Purity of the compounds isolated are not disclosed. The example wherein 97.4% yield is realized is for a specific compound which is also claimed, 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (claim 6). Thus, while Blum does disclose one isolated reaction of very high yield, there is no

evidence that the reaction scheme employed results in a consistently high yield among various species of diphosphonic acid syntheses. To the contrary, Blum employs chlorobenzene, which is the only reaction solvent enabled among the four cited references and which typically results in yields of about 27% to 56% of theory, based on the cited references. This would tend to indicate that the high yield of the single example of Blum was due to some other factor, i.e. the particular reagents used or some other reaction variable.

Jary also claims 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid and employs chlorobenzene as the sole solvent. Yield of the compound is 55% of theory (column 3, line 11).

Bosies discloses that sulfolane can be a diluent; however, its use is not enabled and there is only one mention of sulfolane in the specification. There is no evidence that Bosies contemplates that the use of sulfolane in the reaction of a carboxylic acid with phosphorous trichloride ( $\text{PCl}_3$ ), phosphorous oxychloride ( $\text{POCl}_3$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ) will result in consistently high yields.

In all of the cited references, the only solvent actually employed is chlorobenzene. Sulfolane is not recognized as a chlorobenzene equivalent or substitute. There is nothing in the cited references that teaches or suggests using sulfolane in place of chlorobenzene. There is nothing in the cited references that teaches or suggests using sulfolane in place of chlorobenzene in the reaction of a carboxylic acid with phosphorous trichloride ( $\text{PCl}_3$ ), phosphorous oxychloride ( $\text{POCl}_3$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ). Thus, there could be no reasonable expectation, prior to Applicants' discovery, of success in using sulfolane to realize consistently and significantly improved yields, compared to yields of the cited art, over the wide range of reagent species exemplified by Applicants.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the cited references do not render the presently claimed invention obvious, and withdrawal of this rejection is respectfully requested.

#### Defective Oath or Declaration

The Examiner asserts that the oath or declaration is defective because it is unexecuted by the inventors. However, in consulting PAIR, Applicants have ascertained that the Office has

Reply to Office Action of January 8, 2007

acknowledged receipt of a properly executed Declaration pursuant to the above mentioned application was filed on January 3, 2007 with a communication. A copy of the signed Declaration obtained from PAIR is included with this Response for the convenience of the Examiner.

Applicants believe that they have fulfilled their duty to provide a properly executed Declaration. If the Examiner has some other objection to the Declaration, Applicants respectfully request notice as to its nature.

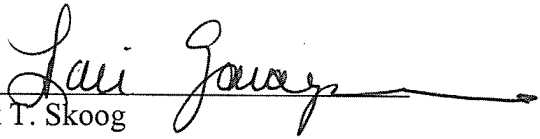
**Summary**

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,  
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Date: \_\_\_\_\_

9 July 2007

  
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**23552**

PATENT TRADEMARK OFFICE

USSN 10/569308

SIGNED DECLARATION

FROM PAIR

Attorney Docket No. 15395.0001USWO

MERCHANT &amp; GOULD P.C.

United States Patent Application

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JAN 03 2007

## COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: A PROCESS FOR PREPARATION OF BISPHOSPHONIC ACID COMPOUNDS

The specification of which

a. ☐ is attached hereto

b. ☒ was filed on \_\_\_\_\_ as (Attorney Docket No. 15395.0001USWO) application serial no. \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/IN2004/000238 filed August 10, 2004 and as amended on \_\_\_\_\_ (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☐ no such applications have been filed.b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
INDIA	837/MUM/2003	21 August 2003	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

U.S. PROVISIONAL APPLICATION NUMBER	DATE OF FILING (Day, Month, Year)

I acknowledge the duty to disclose information that is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (reprinted below):

**§ 1.56 Duty to disclose information material to patentability.**

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

- (1) prior art cited in search reports of a foreign patent office in a counterpart application, and
- (2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

- (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim;

or

- (2) It refutes, or is inconsistent with, a position the applicant takes in:
  - (i) Opposing an argument of unpatentability relied on by the Office, or
  - (ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

- (1) Each inventor named in the application;
- (2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

(e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby appoint the attorney(s) and/or patent agent(s) associated with the following customer number to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith.

**23552**

PATENT TRADEMARK OFFICE


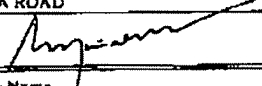

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Merchant & Gould P.C. to the contrary.

I understand that the execution of this document, and the grant of a power of attorney, does not in itself establish an attorney-client relationship between the undersigned and the law firm Merchant & Gould P.C., or any of its attorneys.

Please direct all correspondence in this case to customer number 23552.



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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